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## Eosinopenia is associated with greater severity in patients with coronavirus disease 2019

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To the Editor:

The novel coronavirus (SARS-CoV-2)-infected pneumonia, now known as coronavirus disease 2019 (COVID-19), which began in Wuhan, China, since late December 2019, has now become a public health emergency of international concern.<sup>1</sup> Previous studies indicated that the clinical condition of patients worsened in a short period of time, while a national survey of 1099 cases with COVID-19 suggested that 5% required intensive care and 1.36% succumbed to severe infection.<sup>2</sup> Despite that the available articles have described the clinical features of COVID-19 patients,<sup>1, 3</sup> it is important to emphasize that partial critically ill patients showed poor therapeutic efficiency and worse prognosis and thus clinical diagnosis research is still warrant.

Based on accumulating data,<sup>4,5</sup> patients with severe COVID-19 show a trend towards eosinopenia, which raises the concern whether eosinopenia is associated with the disease severity. Eosinophil, initially identified as a key effector cell of allergy, has now been demonstrated to possess antiviral capacities and serve to amplify immune response and thus dampen inflammation.<sup>6</sup> It is currently not known whether COVID-19 patients with eosinopenia are also more likely to develop into critically illness. This updated analysis aimed to investigate the association between eosinopenia and COVID-19 severity.

This single-center, retrospective study reports 51 laboratory-confirmed COVID-19 patients admitted to Wuhan Tongji Hospital between February 9, 2020 and February 16, 2020, and electronic medical records, including demographics, clinical symptoms and signs, underlying comorbidities, laboratory features on admission were reviewed and analyzed. Severity of COVID-19 was defined based on the guideline issued by Chinese National Health Committee, and eosinopenia is defined as eosinophil absolute number  $< 0.02 \times 10^9$ . This study was approved by the local ethics review board, and informed consents from patients with COVID-19 were waived for use of the de-identified data.

Demographics and partial clinical characteristics of COVID-19 patients stratified by eosinophil status are shown in Table 1. Of 51 patients, 18 (35.3%) patients showed a decrease in eosinophil absolute number. Compared with normal eosinophil group, eosinopenia patients presented serious vital signs on admission, with faster heart rate (101 vs. 87 beats/min,  $p=0.001$ ) and relatively higher temperature (36.4 vs. 36°C,  $p=0.012$ ), and a greater proportion of eosinopenia patients were categorized into a severe condition (66.7 vs. 27.3%,  $p=0.006$ ).

Of 51 patients, the majority experienced lymphopenia and abnormality of neutrophil in the blood routine test (Table S1). Compared with patients with normal eosinophil range, eosinopenia patients tended to present a lower trend in lymphocyte count ( $0.86$  vs.  $1.22 \times 10^9/L$ ,  $p=0.005$ ), monocyte absolute number ( $0.29$  vs.  $0.56 \times 10^9/L$ ,  $p=0.003$ ) and proportion ( $8.1$  vs.  $9.7\%$ ,  $p=0.01$ ) but a higher neutrophil proportion ( $75$  vs.  $66.5\%$ ,  $p=0.043$ ). Furthermore, absolute number of eosinophils were positively correlated with lymphocyte count (Figure 1A), similar to reports by Zhang et al.<sup>5</sup> and Qian et al.<sup>7</sup>, where the correlation was also statistically significant on 3 or more days afterward in Zhang's study ( $r=0.479$ ,  $p<0.001$ ).<sup>5</sup>

Following the inflammatory markers, eosinopenia patients have higher high sensitive C-reactive protein ( $50.5$  vs.  $24.6\text{mg/L}$ ,  $p=0.022$ ) and procalcitonin ( $0.085$  vs.  $0.05\text{ng/dL}$ ,  $p=0.048$ ) concentrations. Particularly, high sensitive C-reactive protein levels inversely correlated with absolute number of eosinophils (Figure 1B). Also, in eosinopenia group, elevated aspartate aminotransferase ( $39$  vs.  $22\text{U/L}$ ,  $p=0.004$ ), blood glucose ( $6.83$  vs.  $5.68\text{mmol/L}$ ,  $p=0.01$ ), creatine kinase ( $135$  vs.  $60\text{U/L}$ ,  $p=0.041$ ) and lactate dehydrogenase ( $356.5$  vs.  $221\text{U/L}$ ,  $p=0.01$ ) were found, whereas lower levels of total cholesterol ( $3.05$  vs.  $3.83\text{ mmol/L}$ ,  $p=0.001$ ) and triglycerides ( $0.77$  vs.  $1.38\text{ mmol/L}$ ,  $p=0.056$ ) were more common in these cases.

To identify the effect of eosinophil on COVID-19 severity, we obtained the odds ratio (OR) after conducting the logistic regression analysis (Table S2). Given blood test was influenced by age, gender and other traditional risk factors, we constructed adjusted models and obtained the adjusted OR. Notably, after controlling confounding factors, the association between eosinopenia and COVID-19 severity remained significant (adjusted-OR  $9.679$ ,  $95\%CI$ :  $1.928$ ,  $48.585$ ,  $p=0.006$ ).

Formerly, eosinophils were regarded as an intermediary factor in the propagation and potentiation of allergic-type process within the host.<sup>6</sup> With the concept emerging, that eosinophils are participating in maintaining immune regulatory systems, eosinophils were increasingly believed to be positioned centrally within inflammatory networks by producing inflammatory and homeostatic mediators. As comprehensively illustrated in "LIAR hypothesis",<sup>8</sup> eosinophils were responsible for local immunity and tissue repair. In animal models, eosinophils were even reported to possess antiviral activity,<sup>9</sup> but it has not been clinically confirmed in humans. In the present study, the findings suggest that eosinopenia was inversely related to inflammatory markers and could be associated with the severity of COVID-19. As shown by recent evidence, eosinopenia was

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very frequent in COVID-19,<sup>10, 11</sup> and could be applied in the early prediction of severity before clinical symptoms have significantly deteriorated, which may help clinicians in identifying potentially severe cases and greatly improve the prognosis of patients with COVID-19. As suggested, eosinopenia may have an important prognostic value in COVID-19 patients, especially in patients with typical radiological images and clinical manifestation.<sup>5, 12-14</sup>

The pathophysiology for eosinopenia in COVID-19 could be multifactorial, involving the suppressed eosinophil egress from the bone marrow, inhibition of eosinophilopoiesis, reduced eosinophil-driving cytokines or direct interferon-induced apoptosis.<sup>15,16</sup> It has been speculated that eosinophil exhaustion was associated with neutralization of virus with eosinophil-derived enzymes, but from another perspective, eosinophil may be just a coincidence when IL-33 pathway was affected by the virus.<sup>17,18</sup> IL-33 is responsible for eosinophil activation locally in the airways and at the bone marrow level,<sup>17</sup> and ciliated epithelial cells, as the first target of coronavirus, are IL-33 positive epithelial cells. Besides, IL-33 is important for the activation of group 2 innate lymphoid cells which produce IL-5 and IL-13,<sup>19</sup> and IL-5 is responsible for eosinophil recruitment to the airways and IL-13 for mucus hypersecretion. However, whether eosinophils might be important for antiviral activity or there is an IL-33 pathway that gets activated and eosinopenia is just coincidence, needs further investigation. Patients included in our study were not accompanied with allergic diseases (e.g. asthma). One possible reason may be our small sample size, but future larger sample research is needed to identify the effect of SARS-CoV-2 on allergic disorders.

#### **Conflicts of interest**

None reported.

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### Figure legend

**Figure 1.** Correlation between eosinophil and lymphocyte counts ( $\times 10^9/L$ ) (A) and correlation between eosinophil counts ( $\times 10^9/L$ ) and high sensitive C-reactive protein levels (mg/L) (B) in blood from COVID-19 patients. Spearman's test was used to evaluate the correlation. hsCRP: high sensitive C-reactive protein.

**Table 1.** Demographic and partial characteristics of patients with laboratory-confirmed COVID-19

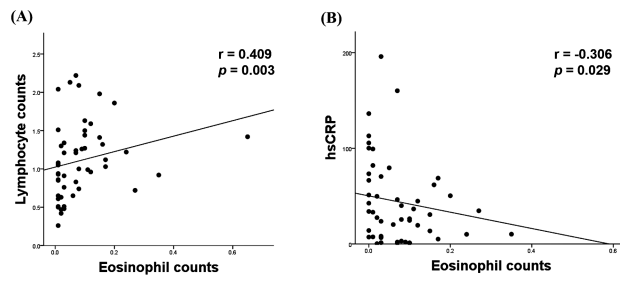
Overall (n=51)	Eosinopenia status		<i>p</i> value
	Without eosinopenia (n=33)	With eosinopenia (n=18)	

<b>Demographics</b>				
Age (years)	63 (51, 68)	63 (54, 68)	63 (46, 72)	0.844
Gender/Female	21 (41)	14 (42.4)	7 (38.9)	0.806
Systolic blood pressure (mmHg)	134 (118, 149)	134 (117, 149)	129 (123, 150)	0.730
Diastolic blood pressure (mmHg)	82 (75, 93)	79 (71, 92)	83 (79, 95)	0.108
Respiratory rate	20 (20, 21)	20 (18, 21)	20 (20, 24)	0.097
Heart rate (beats per minute)	92 (83, 102)	87 (78, 99)	101 (90, 116)	0.001
Temperature on admission (°C)	36 (35.8, 36.5)	36 (35.8, 36.3)	36.4 (36, 37.5)	0.012
Severity <sup>&amp;</sup> -No.	21 (42.3)	9 (27.3)	12 (66.7)	0.006
Smoking history	19 (37)	13 (39.4)	6 (33.3)	0.669
<b>Onset Symptoms</b>				
Fever	40 (78)	26 (78.8)	14 (77.8)	0.933
Fatigue	37 (72.5)	26 (78.8)	11 (61.1)	0.176
Dry cough	30 (58.8)	21 (63.6)	9 (50)	0.344
Nasal congestion	7 (13.7)	5 (15.2)	2 (11.1)	0.689
Shortness of breath	23 (45.1)	15 (45.5)	8 (44.4)	0.945
Rhinorrhea	3 (5.9)	1 (3.0)	2 (11.1)	0.241
Muscle ache	12 (23.5)	7 (21.2)	5 (27.8)	0.597
Diarrhea	15 (29.4)	12 (36.4)	3 (16.7)	0.140
More than one sign or symptom	40 (78.4)	27 (81.8)	13 (72.2)	0.426
<b>Comorbidities</b>				
Any	35 (68.6)	24 (72.7)	11 (61.1)	0.393
Hypertension	21 (41.2)	15 (45.5)	6 (33.3)	0.401
Diabetes	9 (17.6)	8 (24.2)	1 (5.6)	0.094
Cerebrovascular disease	4 (7.8)	1 (3.0)	3 (16.7)	0.083
Coronary artery disease	5 (9.8)	5 (15.2)	0	0.082
Respiratory diseases	8 (15.7)	5 (15.2)	3 (16.7)	0.887
Cancer	7 (13.7)	4 (12.1)	3 (16.7)	0.652

Chronic kidney disease	1 (2.0)	1 (3.0)	0	0.456
Chronic liver disease	8 (15.7)	6 (18.2)	2 (11.1)	0.507
<b>Clinical outcomes</b>				0.168
Discharge	45 (88.2)	31 (93.9)	14 (77.8)	—
Death	6 (11.8)	2 (6.1)	4 (22.2)	—

Results were presented as median (IQR) for continuous variables and number (%) for categorical variables. Parameters between with and without eosinopenia groups were tested by Mann-Whitney U test (continuous variables) or Chi-square test (categorical variables). A two-sided  $p$  of less than 0.05 was considered statistically significant.

& Severe cases at admission met at least one of the following items: (1): breathing rate  $\geq 30/\text{min}$ ; (2) oxygen saturation at rest state  $\leq 93\%$ ; (3) partial pressure of arterial oxygen ( $\text{PaO}_2$ )/fraction of inspired oxygen ( $\text{FiO}_2$ )  $\leq 300\text{mmHg}$  ( $1\text{mmHg}=0.133\text{kPa}$ ).



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